Neonatal morbidity in singleton late preterm infants compared with full-term infants

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Abstract: Aim: The aim of this study was to test the hypothesis that singleton late preterm infants (34 0/7 to 36 6/7 weeks of gestation) compared with full-term infants have a higher incidence of short-term morbidity and stay longer in hospital. Methods: In this retrospective, multicentre study, electronic data of children born at five hospitals in Switzerland were recorded. Short-term outcome of late preterm infants was compared with a control group of full-term infants (39 0/7 to 40 6/7 weeks of gestation). Multiple gestations, pregnancies complicated by foetal malformations, maternal consumption of illicit drugs and infants with incomplete documentation were excluded. The results were corrected for gender imbalance. Results: Data from 530 late preterm and 1686 full-term infants were analysed. Compared with full-term infants, late preterm infants had a significant higher morbidity: respiratory distress (34.7% vs. 4.6%), hyperbilirubinaemia (47.7% vs. 3.4%), hypoglycaemia (14.3% vs. 0.6%), hypothermia (2.5% vs. 0.6%) and duration of hospitalization (mean, 9.9 days vs. 5.2 days). The risk to develop at least one complication was 7.6 (95% CI: 6.2-9.6) times higher among late preterm infants (70.8%) than among full-term infants (9.3%). Conclusion: Singleton late preterm infants show considerably higher rate of medical complications and prolonged hospital stay compared with matched full-term infants and therefore need more medical and financial resources.

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Neonatal Morbidity in Singleton Late Preterm Infants Compared With Full-Term Infants

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KEYWORDS:

Late preterm, Morbidity, Near term, Outcome, Perinatal

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Abstract

Aim: To test the hypothesis that singleton late preterm infants (34 0/7 to 36 6/7 weeks of gestation) compared with full-term infants have a higher incidence of short-term morbidity and stay longer in hospital.

Methods: In this retrospective, multi-centre study electronic data of children born at five hospitals in Switzerland were recorded. Short-term outcome of late preterm infants were compared with a control group of full-term infants (39 0/7 to 40 6/7 weeks of gestation). Multiple gestations, pregnancies complicated by fetal malformations, maternal consumption of illicit drugs and infants with incomplete documentation were excluded. The results were corrected for gender imbalance.

Results: Data from 530 late preterm and 1686 full-term infants were analysed. Compared with full-term infants, late preterm infants had a significant higher morbidity: respiratory distress (34.7% versus 4.6%), hyperbilirubinaemia (47.7% versus 3.4%), hypoglycaemia (14.3% versus 0.6%), hypothermia (2.5% versus 0.6%), duration of hospitalization (mean 9.9 days versus 5.2 days). The risk to develop at least one complication was 7.6 (95% CI: 6.2 – 9.6) times higher among late preterm infants (70.8%) than full-term infants (9.3%).

Conclusion:

Singleton late preterm infants show considerably higher rate of medical complications and prolonged hospital stay compared with matched full-term infants and therefore need more medical and financial resources.

Key notes

Late preterm singletons (34 0/7 to 36 6/7 gestational weeks) show significantly higher rate of medical complications and prolonged hospital stay compared with full-term infants matched for gender and therefore need more medical and financial resources. The risk to develop at least one complication is 7.6 (95% CI: 6.2 – 9.6) times higher and the mean duration of hospital stays is 1.9 (95% CI: 1.5 to 2.3) times longer among late preterm infants.

Introduction

In the last decades many obstetric and neonatal management strategies have been developed in order to decrease the mortality and morbidity of preterm infants. These strategies include interventions such as tocolytic drugs, antenatal lung maturation and the foundation of perinatal centres with integrated maternal, fetal and neonatal management favouring in utero-transfers of high risk pregnancies (1). These efforts, among others, benefit foremost preterm infants born before 32 weeks of gestation. Compared to very preterm infants, late preterm infants, i.e. infants born between 34 0/7 and 36 6/7 weeks of gestation (2), were considered to be of lower scientific interest. However, in recent years, some concern rose in the literature because of the longer hospital stay and the higher costs of the latter group. Simultaneously, an increase in the rate of late preterm deliveries was observed over the last two decades (3), another reason why attention focused on their short-term and long-term outcome (1, 4-8).

Late preterm infants are often cared for in level I newborn nurseries and stay with their mothers after delivery (9). Yet, they are physiologically and metabolically immature (2, 8, 10). Consequently, they are at a higher risk for morbidity when compared with full-term infants (4, 7, 10, 11), such as respiratory distress (8, 12-14), hyperbilirubinaemia (8, 15-17), temperature instability (8, 18), feeding difficulties (8, 19, 20), hypoglycaemia (8, 18) and need for NICU admission (7, 8, 21).

Several studies performed in recent years shaped the awareness that late preterm infants need more medical interventions than full-term infants due to their immaturity (22). Subsequently, lower limits for interventions were determined for this population. In Switzerland 5 to 6% of all newborn infants are born between 34 and 36 weeks of gestation with an increasing trend over the last years (2). This trend is believed to be associated with the raised mean age of primiparous women leading to a higher rate of complications, the increased use of assisted reproductive technologies leading to an increase in multifetal pregnancies known to be associated with a shorter gestational age (23, 24) and the increasing trend for elective caesarian sections in the late preterm period. The advances in obstetric practice causing an increase in surveillance and medical interventions during this period may also play a role (22, 25, 26). Infants considered at risk are identified earlier which results in more deliveries in the late preterm period. In addition the progress in medical practice to delay the delivery could possibly lead to a shift from deliveries of very preterm infants into deliveries of late preterm infants (22-25, 27).

In accordance with the guidelines of the Swiss Society of Neonatology (SGN), infants from 34 0/7 weeks of gestation can be delivered in level I nursery care units lacking a centre-gated NICU provided trained personnel and adequate equipment is available (28). Should a prenatal complication compromise mother's or child's health, intrauterine transfer to a perinatal centre with a neonatal unit needs to be considered.

The first goal of this study was to quantify the risk for short-term morbidity in singleton late preterm infants compared with full-term infants. The second goal was to assess the duration of hospitalization of the study and the control group which is directly related to cost in our health system.

Methods

In this retrospective multi-centre study electronic anonymous data were recorded for all late preterm deliveries (34 0/7 to 36 6/7 weeks of gestation) from January 2006 to December 2007 at the University Hospital of Zurich and its four surrounding hospitals: Zollikerberg, Triemli, Limmattal, and Uster. The University Hospital Zurich has a nursery and a level III neonatal intensive care unit, Zollikerberg and Triemli each have a nursery and a level II neonatal care unit, and Limmattal and Uster have a level I newborn nursery care unit. The study group was compared with a control group consisting of full-term infants (39 0/7 to 40 6/7 weeks of gestation) from the University Hospital Zurich. Data concerning the infants' complications were obtained from discharge records, made anonymous and recorded in an electronic database. In all five hospitals the same variables priorly defined for the national health statistics were used.

Pregnancies complicated by any of the following conditions were excluded from both the study and the control group: multiple gestations, fetal malformations, maternal consumption of illicit drugs, and infants with incomplete documentation. We documented gestational age, preeclampsia, maternal gestational diabetes, mode of delivery, birth weight, growth restriction (weight, length and head circumference below 3rd percentile) (30), as well as following clinical diagnoses: respiratory distress with or without oxygen delivery, hyperbilirubinaemia, hypoglycaemia, hypothermia, apnea/bradycardia, feeding problems and duration of hospitalization. We did not exclude infants who were delivered by caesarean section because caesarean section is often chosen as a result of prematurity and this allowed us to evaluate the effect of this mode of delivery on late preterm infants. Neither did we exclude infants with operative delivery (vacuum or forceps extraction), umbilical artery pH below 7.10, 5 minutes Apgar score below 7, other alert signs during and/or after delivery, neonatal sepsis confirmed by positive blood cultures, nor intraventricular haemorrhage (grades 1-4). We did neither exclude pregnancies with preeclampsia, gestational diabetes or preterm premature rupture of

membranes because these conditions often induce late preterm deliveries and thus also need to be observed. Accordingly to those criteria described above our observation period and recruitment of the infants started already before delivery.

For the purpose of the present study, respiratory distress was defined as the presence of transient/isolated tachypnoea of duration longer than 4 hours after delivery, need for oxygen after the fourth hour of life, or the application of mechanical ventilation or nasal CPAP (continuous positive airway pressure) during the first 72 hours after delivery. Hyperbilirubinaemia was defined as jaundice requiring as least phototherapy, hypoglycaemia as a glucose value lower than 2.5 mmol/l (45 mg/dl), and hypothermia as a core body temperature of less than 36.0° Celsius requiring a transfer to a neonatal unit.

We further differentiated between infants with complications (as defined above) and children without. Among the infants with complications, we assessed the number of complications a newborn infant encountered during hospitalization. Infants with feeding problems and apnea/bradycardia were excluded from these latter two evaluations as some of them had no record on whether their condition was severe enough to require transfer to a neonatal unit. Duration of hospitalisation was calculated from date of birth to discharge home.

An unequal ratio of gender between both groups may distort the results as medical condition at birth can be gender related. For that reason we matched both groups to create an equal ratio and excluded gender as a confounding factor for our analysis.

Statistical analyses were performed using SPSS statistical software version 18 (SPSS Inc., Chicago, IL). Comparisons among the late preterm group as well as between late preterm and full-term group were performed using Pearson's Chi-square and/or Fisher's exact tests for proportions. For non-normally distributed continuous variables, the Kruskal-Wallis test for independent samples was used for comparisons among the late preterm group and the Mann-Whitney U-test for comparisons between late preterm and term infants. Probability levels below 0.05 were considered significant.

Results

During the 2-year study period we enrolled 553 late preterm infants in the study group with a mean gestational age of 35 5/7 weeks (range 34 0/7 to 36 6/7 weeks) and 1689 full-term infants in the control group with a mean gestational age of 39 6/7 weeks (range 39 0/7 to 40 6/7 weeks). The study group represents 44.6% (n=553) of all preterm infants (n=1240) and 4.1% of all newborns (n=13'381) during the observation period in the investigating centres. 23 infants (4.16%) of the study group and 3 infants (0.18%) of the control group were excluded due to missing data or ineligibility according to our exclusion criteria. 530 infants for the study group and 1686 infants for the control group were analysed. The demographic and obstetric characteristics of the study and control groups are summarised in table 1. The study group consisted of 59.1% (n=313) males, the control group of 53.1% (n=895, p=0.016). As the male gender is associated with elevated morbidity, we matched in a randomised manner both groups to create a comparable composition of the gender. After excluding 172 female infants in the control group, we had 59.1% male infants in both groups. Using multivariable logistic regression analysis after matching both groups, the unequally distributed factor male gender shows no association with an increased risk for neonatal morbidity that could distort our results. Thus, a further use of the matched and therefore reduced database is no longer necessary for the purpose of this study.

Apgar score values, umbilical artery pH and neonatal/subpartal alert signs showed no difference between both groups. Caesarian section was performed 2.3 (95% CI: 2.0-2.6) times more often in the study group (n=259) than in the control group (n=363) with 48.9% versus 21.5% (p<0.001). The mean birth weight was 2594 g (range 1100 to 4370 g) in the study group and 3489 g (range 2290 to 5080 g) in the control group. There was no significant difference for growth restriction between the groups (p=0.54).

Table 1 presents the demographic characteristics in the late preterm and full-term groups. Table 2 and figure 1 shows the neonatal morbidity which is significantly higher ($p<0.001$) in the study group for all analysed diagnoses.

The most frequently recorded adverse outcome in the study group was hyperbilirubinaemia (47.7%; 95% CI: 42.5%-52.1%), followed by respiratory distress (34.7%; 95% CI: 30.8%-38.9%), hypoglycaemia (14.3%; 95% CI: 11.7%-17.5%), feeding problems (8.3%; 95% CI: 6.0%-10.8%) and apnea/bradycardia (7.2%; 95% CI: 5.1%-9.5%). The risk for respiratory distress was 7.5 (95% CI: 5.9-9.6) times higher in the late preterm group than in the full-term group, 14.1 (95% CI: 10.8-18.5) times higher for hyperbilirubinaemia, 24.2 (95% CI: 12.6-46.4) times higher for hypoglycaemia and 4.1 (95% CI: 1.8-9.4) times higher for hypothermia. Late preterm infants were 7.4 (95% CI: 5.1-10.6) times more likely oxygen dependant and needed 9 (0.45 vs 0.05 days; 95% CI: 7.3-10.7; $p<0.001$) times more oxygen days than full-term infants. The mean duration of hospital stays was 1.9 times (9.9 vs 5.2 days; 95% CI: 1.7-2.2; $p<0.001$) longer in the study group than in the controls (Figure 2).

Within the study group, neonatal morbidity rates decreased significantly from 34 to 36 weeks of gestation, except for hypothermia ($p=0.23$) where no occurrence was observed in the group with 34 weeks gestational age (Figure 3).

The probability to have at least one diagnosed medical condition (variable 'complication') was 7.6 (95% CI: 6.5-9.0) times higher in the study group than in the control group. The mean complications ratio (measured as mean count of medical diagnoses including respiratory distress, hyperbilirubinaemia, hypoglycaemia and hypothermia) was 1.08 (95% CI: 1.00-1.15; SD 0.907) for the study group and 0.1 (95% CI: 0.09-0.12; SD 0.333) for the control group. That means that late preterm infants showed 10.8 (95% CI: 9.6-11.1) times more complications than full-term infants.

Discussion

We found a higher rate of medical complications in late preterm compared to full-term infants than previously published (1, 4, 10, 13, 24, 33). In the present study, late preterm singletons stayed in hospital as twice as long as full-term infants. Those differences may be explained by a different methodology or a different population. The large impact on the need for medical and economic resources remains the same regardless of the cause.

Comments to the methodology

As the main ***selection criterion*** for both the study and the control group is gestational age, its accurate assessment was critical. In our study population 98% of the gestational age assessments were based on an ultrasound examination in the early phase of pregnancy between 11 – 14 weeks of gestation with a 95% confidence interval of 5 to 7 days (31).

For the control group the gestational age range between 39 0/7 and 40 6/7 weeks with the lowest risk for adaptational problems was chosen. This goes in line with severel recent reports suggesting to divide the 5 week range for term infants in two parts based on different risk for respiratory and other problems (29).

Exclusion criteria may affect the incidence of specific conditions. In accordance with Melamed et al (4) but in discordance with Wang et al (8) and Dani et al (11) we excluded twins and higher order multiplets as these infants have a higher risk for growth retardation and complications independent of gestational age than singletons. The predefined exclusion criteria such as severe malformation and illicit substance abuse were not applicable to either cohort. In contrast to the study of Melamed et al (4), we did not exclude pregnancy complications such as preeclampsia, gestational diabetes, preterm premature rupture of membranes, growth restriction, oligohydramnion and other perinatal alert signs as these conditions may be gestational age dependent. 4.2% of the infants were excluded due to

incomplete data in the study group and 0.6% in the control group. Although this difference is statistically significant, it does not corroborate the main findings.

The ***definitions of medical complications*** are crucial for the assessment of incidence and prevalence. For respiratory distress, hypoglycaemia and hypothermia, well established definitions (28), identical for late preterm and full-term infants, were used. Hyperbilirubinaemia was defined differently for both groups as intervention levels are lower for late preterm infants. This difference is justified by the fact that late preterm infants are more vulnerable to high serum bilirubin levels.

In this study, the male-female ratio was higher in the control group than in the study group. After matching both groups to create an equal gender ratio, the unequally distributed factor male gender shows no increased risk for neonatal morbidity by multivariable logistic regression. We could therefore eliminate this disturbing factor for our results. The fact that no infant of 34 weeks gestation had hypothermia is not surprising, as, in accordance with the recommendations from the Swiss Society of Neonatology (28), they are usually placed into a heated bed to prevent hypothermia. Likewise, infants with a second medical diagnosis, such as oxygen dependant respiratory distress, may have been placed into an incubator and thus precluding hypothermia.

Comment to the study population

To ensure that our study population is representative we collected data from hospitals of different care levels. The proportion of late preterm singletons to all lifeborns was 4.1% for the whole study group. This corresponds well to the percentage of late preterm singletons in Switzerland, which is 4.3%. In other countries and populations the proportion of late preterm singletons is reported to rise up to 8.8% with increasing trend (3). This fact may affect the incidence of complications.

Strengths of this paper are the use of predefined definitions, the inclusion of nurseries and NICUs of different levels, a control group of full-term infants, the minimal number of exclusion criteria, the adjustment of the data for inequality in gender distribution and a large population size and therefore statistical power. ***Weaknesses*** are the retrospective analysis (partly compensated by prospectively planned data collection), the exclusion of infants with incomplete data and lack of long-term outcome.

Conclusion

The more than sevenfold complication risk of late preterm singletons compared to matched full-term controls is of concern for health professionals and parents. Strategies to reduce this significant health burden must include both obstetricians and neonatologists. Delivery before 37 completed weeks should only be considered for strict maternal and/or fetal indication. As the complication rate at 34 completed weeks almost reaches 100%, delivery of these infants in a level II or III unit is mandatory in order to avoid the need for postnatal transfer to a neonatal unit with separation from the mother.

The prolonged hospital stay of late preterm infants by almost 50% has an economic impact and should be taken into account for DRGs (Diagnosis Related Groups).

Given the high rate of acute complications in late preterm infants, there is a need for assessment of long-term outcome of this risk group.

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Tables and Figures

Table 1: Demographic characteristics of late preterm infants (study group, n=530) and full-term infants (control group, n=1686).

	Late preterm infants (n=530)						
	34 wk (n= 115)	**35 wk (n= 153)**	**36 wk (n= 262)**	***P*** [1]	**Late preterm (n=530)**	**Full term (n=1686)**	***P*** [2]
Gestational age at delivery (wk)	34 2/7	35 3/7	36 3/7	-	35 5/7	39 6/7	-
Preeclampsia	10 (8.7)	7 (4.6)	7 (2.7)	*0.035*	24 (4.5)	11 (0.7)	*<0.001*
Gestational diabetes	4 (3.5)	0 (0.0)	4 (1.5)	*0.32*	8 (1.5)	8 (0.5)	*0.014*
Gender, male	62 (53.9)	90 (58.8)	161 (61.5)	*0.39*	313 (59.1)	895 (53.1)	*0.016*
Caesarean delivery	72 (62.6)	65 (42.5)	122 (46.6)	*0.003*	259 (48.9)	363 (21.5)	*<0.001*
Delivery by forceps extraction	2 (1.7)	0 (0.0)	0 (0.0)	*0.023*	2 (0.4)	1 (0.1)	*0.14*
Delivery by vacuum extraction	1 (0.9)	7 (4.6)	14 (5.3)	*0.13*	22 (4.2)	246 (14.6)	*<0.001*
Spontaneous delivery	40 (34.8)	81 (52.9)	126 (48.1)	*0.010*	247 (46.6)	1076 (63.8)	*<0.001*
Apgar score (mean)	8/9/9	8/9/9	8/9/9	-	8/9/9	8/9/9	-
pH of umbilical artery (mean)	7.30	7.28	7.27	-	7.28	7.27	-
Subpartal and neonatal alert signs	15 (13.0)	22 (14.4)	29 (11.1)	*0.60*	66 (12.5)	378 (22.4)	*<0.001*
Birth weight in g (mean)	2251	2535	2779	-	2594	3489	-
- weight < 3rd percentile	7 (6.1)	7 (4.6)	14 (5.3)	*0.86*	28 (5.3)	78 (4.6)	*0.54*
- length < 3rd percentile	7 (6.1)	11 (7.2)	17 (6.5)	*0.93*	35 (6.6)	114 (6.8)	*0.90*
- microcephaly (< 3rd percentile)	9 (7.8)	5 (3.3)	9 (3.4)	*0.12*	23 (4.3)	43 (2.6)	*0.035*

Data are expressed as number and proportion (%). Birth weight, Apgar score and pH of umbilical artery as mean value.

P [1] Refers to comparison of late preterm subgroups: comparison of 34, 35 and 36 weeks of gestation.

P [2] Refers to comparison of late preterm compared with full-term infants.

Table 2: Neonatal morbidity of late preterm infants (study group) and full-term infants (control group).

	Late preterm infants (n=530)						
	34 wk (n= 115)	**35 wk (n= 153)**	**36 wk (n= 262)**	***P*** [1]	**Late preterm (n=530)**	**Full term (n=1686)**	***P*** [2]
Respiratory distress (RD)	73 (63.5)	56 (36.6)	55 (21.0)	*<0.001*	184 (34.7)	78 (4.6)	*<0.001*
Oxygen dependency	37 (32.2)	27 (17.6)	24 (9.2)	*<0.001*	88 (16.6)	38 (2.3)	*<0.001*
Oxygen days (mean)	0.97	0.56	0.15	*<0.001*	0.45	0.05	*<0.001*
- Oxygen days by infant with RD	1.42	1.52	0.71	*0.45*	1.24	0.85	*0.46*
- Oxygen days by infant with oxygen dependency	3.03	3.15	1.63	*0.08*	2.68	1.39	*0.014*
Mechanical ventilation	7 (6.1)	5 (3.3)	4 (1.5)	*0.018*	16 (3.0)	4 (0.2)	*<0.001*
CPAP	12 (10.4)	8 (5.2)	6 (2.3)	*0.003*	26 (4.9)	2 (0.1)	*<0.001*
Hyperbilirubinaemia	68 (59.1)	73 (47.7)	112 (42.7)	*0.014*	253 (47.7)	57 (3.4)	*<0.001*
Hypoglycaemia	29 (25.2)	22 (14.4)	25 (9.5)	*<0.001*	76 (14.3)	10 (0.6)	*<0.001*
Hypothermia	0 (0.0)	6 (3.9)	7 (2.7)	*0.23*	13 (2.5)	10 (0.6)	*<0.001*
Apnea and bradycardia [i]	16 (13.9)	15 (9.8)	7 (2.7)	*<0.001*	38 (7.2)	11 (0.7)	*<0.001*
Feeding problems [i]	22 (19.1)	17 (11.1)	5 (1.9)	*<0.001*	44 (8.3)	17 (1.0)	*<0.001*
Complications *	105 (91.3)	114 (74.5)	156 (59.5)	*<0.001*	375 (70.8)	156 (9.3)	*<0.001*
Complications ratio *(± SD)* **	1.7 *(±0.905)*	1.14 *(±0.911)*	0.78 *(±0.761)*	*<0.001*	1.08 *(±0.907)*	0.1 *(±0.333)*	*<0.001*
Hospitalization, days (mean)	13.6	12.1	7.0	*<0.001*	9.9	5.2	*<0.001*

Data are expressed as absolute numbers and proportions (%). Oxygen days and hospitalization days as mean value. Complications ratio as mean value ± standard deviation (± SD).

** Complications: Infants with at least one medical condition diagnosed absolute and in percent.*

*** Complications ratio (composite): Number of medical condition diagnosed per infants expressed as a ratio (n).*

[i] Were not included in the complications and complications ratio.

P [1] Refers to comparison of late preterm subgroups: comparison of 34, 35 and 36 weeks of gestation.

P [2] Refers to comparison of late preterm with full-term children.

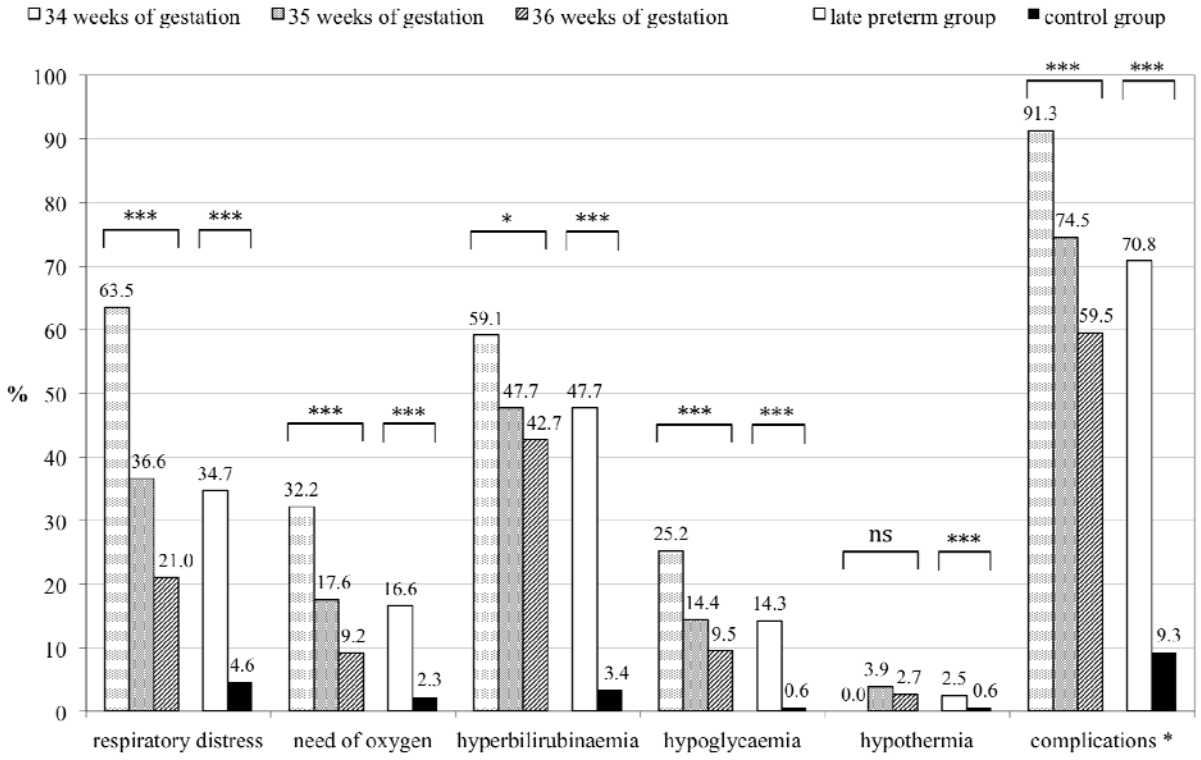

Figure 1: Distribution of morbidity of late preterm infants (study group) and full-term infants (control group 39 and 40 gestational weeks) in percent. We assessed respiratory distress with and without oxygen dependency, hyperbilirubinaemia, hypoglycaemia, hypothermia. Complications refers to the number of infants who had at least one medical condition diagnosed that was responsible for a mother-child separation with subsequent treatment in a neonatal unit.

Legend: ns not significant, * $p<0.05$, ** $p<0.01$, *** $p<0.001$.

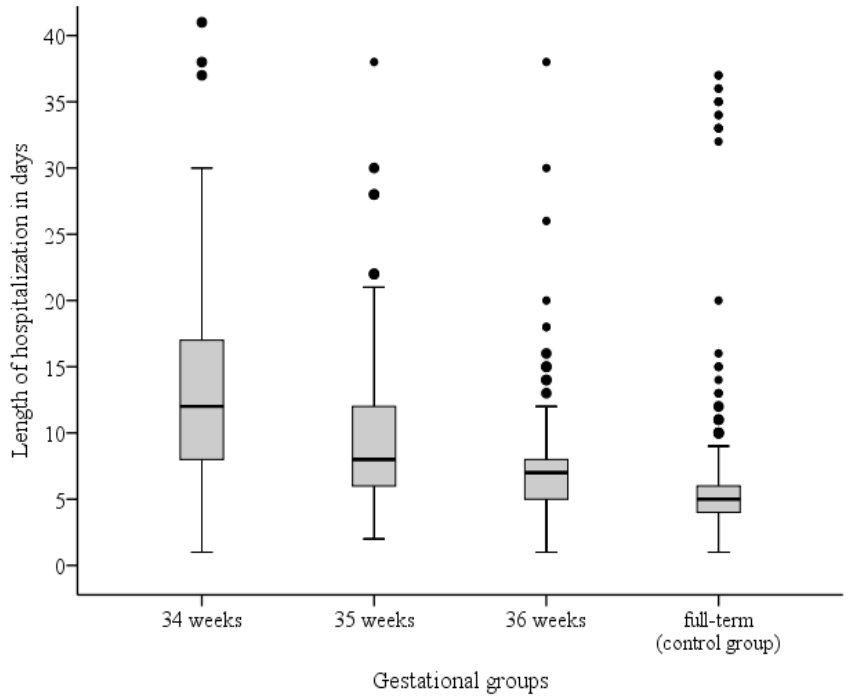

Figure 2: Morbidity by the length of hospitalization of late preterm (study group) and full-term infants (control group 39 and 40 gestational weeks). The figure displays the mean length of hospital stay (95% CI; ± 2 SD) by gestational age groups (34 to 36 weeks) and control group of full-term ($p<0.001$).

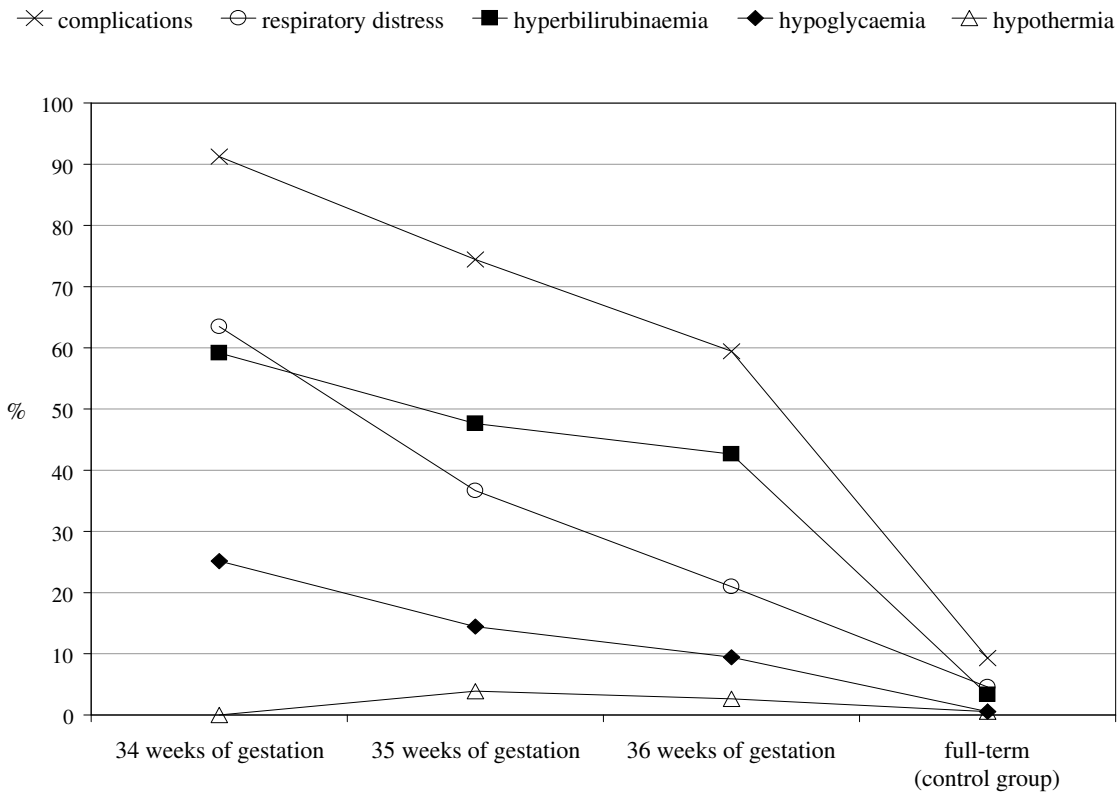

Figure 3: Rate of neonatal morbidity in percent by gestational week in late preterm (study group) and full-term infants (control group 39 and 40 gestational weeks). The meaning of "complications" is the percentage of infants with at least one medical condition out of respiratory distress, hyperbilirubinaemia, hypoglycaemia and hypothermia ($p<0.001$).